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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,390	07/29/2005	Yong-Hoon Chung	5252MC-1	7628

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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/519,390	CHUNG ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-74* is/are pending in the application.

4a) Of the above claim(s) *43-61 and 63-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-42 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/23/04, 9/7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of claims 38-42 and 62, drawn to a protein variant, with species elections to the 4-alpha helix bundle cytokine thrombopoietin (TPO) corresponding to SEQ ID NOL: 25, in the reply filed on 15 September 2006 is acknowledged.

2. Claims 38-74 are pending. Claims 43-61 and 63-74 are withdrawn from consideration as being drawn to a non-elected invention. Claims 38-42 and 42 are under examination.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 23 December 2004 and 7 September 2005 have been fully considered. A signed copy of the IDS statements are attached.

Specification – Objections

4. The use of the trademarks STRATGENE (p. 36), TRITON X-100 (p. 36), PROMEGA (p. 36 and 53), QIAGEN (p. 36), PBLUESCRIPT KS (p. 36 and 39), INVITROGEN (p. 36), SIGMA (p. 36 and 52), CALBIOCHEM (p. 49), and PHARMACIA (p. 49) have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Protein variants of TPO.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 38-42 and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for TPO muteins F46V, F128V, F131V, F141V, and F148V, and EPO muteins F48V, F138V, F141V, and F148V, does not reasonably provide enablement for all protein variants, cytokine variants, and 4-alpha helix bundle cytokines comprising a substitution of valine for phenylalanine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims recite a protein variant which substitutes a valine residue for a phenylalanine residue in a protein having a biological response-modifying function by binding to a receptor; wherein the protein is a cytokine; wherein the cytokine is a 4-alpha helix bundle cytokine, wherein the 4-alpha helix bundle cytokine is selected from the recited group [thrombopoietin (TPO), as elected]; wherein the recited group [TPO, as elected] are altered by substituting valine for phenylalanine residue[s] of amino acid residues [sic] between positions 110 and 180; wherein the TPO is altered by substituting valine for phenylalanine at a position 46,128,131,141,184,204,240,or 286 of an amino acid sequence designated as SEQ ID NO: 25.

The nature of the invention is drawn to protein muteins comprising non-conservative mutations of phenylalanine to valine. The level of skill of those in the art is related to the incorporation of non-conservative amino acid substitutions in protein chemistry.

The disclosure teaches TPO muteins F46V, F128V, F131V, F141V, and F148V, and EPO muteins F48V, F138V, F141V, and F148V. However, the assertion that all phenylalanine to valine substitution muteins of all protein variants, cytokine variants, and 4-alpha helix bundle cytokines have biological activities similar to the TPO muteins F46V, F128V, F131V, F141V, and F148V, and EPO muteins F48V, F138V, F141V, and F148 taught in the instant disclosure (see, for example, p. 54) cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for

vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF- β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a

function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Moreover, the biological activities of the TPO and EPO muteins disclosed in Tables 9 and 10 (p. 54) show vastly different biological activities, depending on which of the phenylalanine residues are mutated. Some of the residues, for example, TPO-F128V, have a decrease in activity compared to wild-type TPO, whereas TPO-F141V has a greatly increased activity.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed protein variants comprising a phenylalanine to valine substitution to make biologically active protein muteins without resorting to undue experimentation to determine what the specific biological activities of the protein mutants are.

The specification does not teach the skilled artisan how to use the claimed protein variant comprising a valine for phenylalanine non-conservative substitution for purposes unrelated to the asserted biological activity. For example, there is no evidence of tissue-specific expression patterns, such that the polynucleotides encoding polypeptide mutein could be used as a tissue-specific marker. Similarly, there is no disclosure of particular disease states correlating to an alteration in levels or forms of the protein muteins for proteins other than TPO and EPO (as taught on page 54 of the instant disclosure), such that the claimed polypeptide variants could be used as a diagnostic tool. Therefore, the skilled artisan is not provided with sufficient guidance to use the claimed protein variants for any purpose.

Due to the large quantity of experimentation necessary to determine an activity or property of the disclosed protein substitution muteins such that it can be determined how to use the claimed protein substitution muteins, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which fail to recite particular biological activities and also embrace a broad class of structural fragments and variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

8. Claims 38-42 and 62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims recite a protein variant which substitutes a valine residue for a phenylalanine residue in a protein having a biological response-modifying function by binding to a receptor; wherein the protein is a cytokine; wherein the cytokine is a 4-alpha helix bundle cytokine, wherein the 4-alpha helix bundle cytokine is selected from the recited group [TPO, as elected]; wherein the recited group [TPO, as elected] are altered by substituting valine for phenylalanine residue[s] of amino acid residues [sic] between positions 110 and 180; wherein the TPO is altered by substituting valine for phenylalanine at a position 46,128,131,141,184,204,240,or 286 of an amino acid sequence designated as SEQ ID NO: 25.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., protein variants, cytokine variants, and 4-alpha helix bundle cytokines comprising a substitution of valine for phenylalanine.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a

generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There is a single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* TPO muteins F46V, F128V, F131V, F141V, and F148V, and EPO muteins F48V, F138V, F141V, and F148V. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. Moreover, the biological activities of the TPO and EPO muteins disclosed in Tables 9 and 10 (p. 54) show vastly different biological activities, depending on which of the phenylalanine residues are mutated. Some of the residues, for example, TPO-F128V, have a decrease in activity compared to wild-type TPO, whereas TPO-F141V has a greatly increased activity.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which are protein variants, cytokine variants, and 4-alpha helix bundle cytokines comprising a substitution of valine for phenylalanine. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, Second Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 38-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42 recites the protein variant of claim 41 wherein the member of the recited group [TPO, as elected] are altered by substituting valine for phenylalanine residue of amino acid residues [sic] between positions 110 and 180. The phrase "residue of amino acid residues [sic] between positions 110 and 180" is not limited to a particular TPO protein. It is unclear from either the claims or the specification whether "positions 110 and 180" refer to a thrombopoietin protein with or without a signal sequence attached. Additional confusion would occur if TPO were conjugated to a fusion protein. If Applicant wishes to recite a range of amino acids in which a substation mutation is to occur, Applicant should do so with respect to a protein with a known, fixed sequence, for example, SEQ ID NO: 25.

11. Claims 38-41 and 62 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 62 recites the protein variant of claim 41 wherein the TPO is altered by substituting valine for phenylalanine at a position 46, 128, 131, 141, 184, 204, 240,or 286 of an amino acid sequence designated as SEQ ID NO: 25. The phrase "of an amino acid sequence designated as SEQ ID NO: 25" is indefinite as written because the use of the article "an" and the breadth of the claim, as written, causes the claim to read on any protein designated as SEQ ID NO: 25. If Applicant's intention is to limit the SEQ ID NO: 25 to the SEQ ID NO: 25 of the instant case, the claim may recite "position 46, 128, 131, 141, 184, 204, 240,or 286 of SEQ ID NO: 25."

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 38 is rejected under 35 U.S.C. 102(b) as being anticipated by Smulevich et al., (Biochemistry 1994; 33(23):7398-7407).

The claim recites a protein variant which substitutes a valine residue for a phenylalanine residue in a protein having a biological response-modifying function by binding to a receptor.

Smulevich et al., teach F41V in recombinant horseradish peroxidase C (p. 7398, abstract).

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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